III. AMENDMENTS TO THE CLAIMS

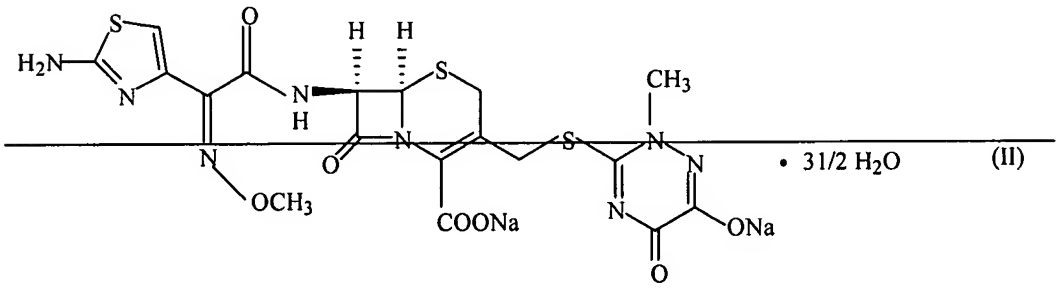
- *PLEASE FIND BELOW A MARKED VERSION OF CLAIMS WITH PRESENT STATUS DELINEATED*

    - *THE CLAIMS ARE HEREIN AMENDED, CANCELLED, OR ADDED TO, SO AS TO EVENTUATE IN THE NEW SET OF PENDING CLAIMS INDICATED BELOW. THIS LISTING OF CLAIMS WILL REPLACE ALL PRIOR VERSIONS AND LISTING OF CLAIMS IN THE APPLICATION.*

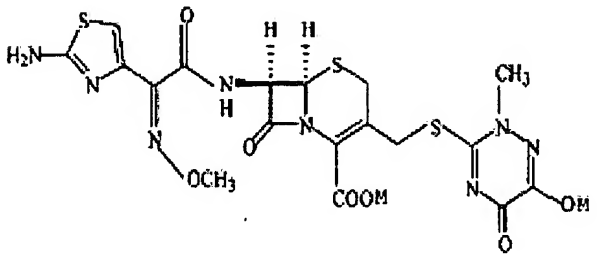
-- The status of each claim is indicated after the claim number by use of a parenthetical identifier selected from: (Original), (Currently amended), (Canceled), (Withdrawn), (Withdrawn – currently amended), (Previously presented), (New), and (Not entered). Claim text is provided for each claim in the listing except for the claims status "canceled" or "not entered." Only claims having the status of "Currently amended" or "Withdrawn – currently amended" include markings to indicate changes that have been made relative to the immediate prior version of the claims. The text of any deleted matter is shown by strike-through, except that double brackets placed before and after deleted characters of five or fewer consecutive characters may be used. The text of any added subject matter is shown by underlining the added text. Claims that were previously canceled that are reinstated here, if any, are reinstated by adding the claim as a "(New)" claim with a new claim number.

COMPLETE LIST OF CLAIMS THAT ARE OR HAVE BEEN BEFORE THE OFFICE
AFTER ENTRANCE OF THE AMENDMENTS MADE HEREIN

Claim 1: (Currently Amended) In a process for preparation of ceftriaxone sodium of formula (II),



• 31/2 H_2O (II)



• 31/2 H_2O (II)

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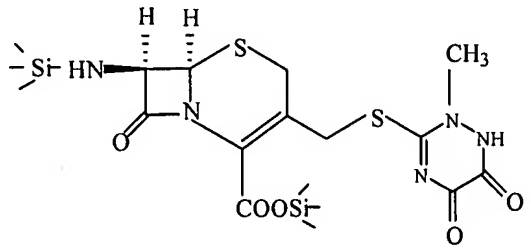
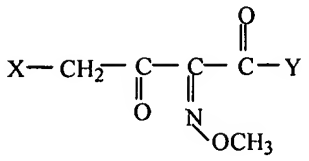
comprising the steps of

i) reacting a silylated compound of formula (III),



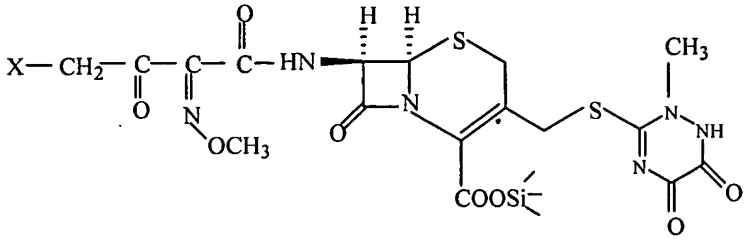
(III)

with a 4-halo-2-methoxyimino-3-oxo-butyric acid derivative of formula (IV),



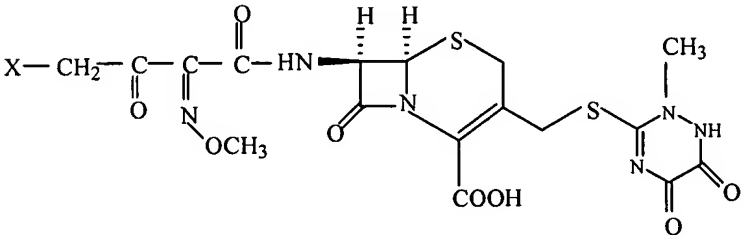
(IV)

wherein X and Y represent a halogen atom to give a compound of formula (V),



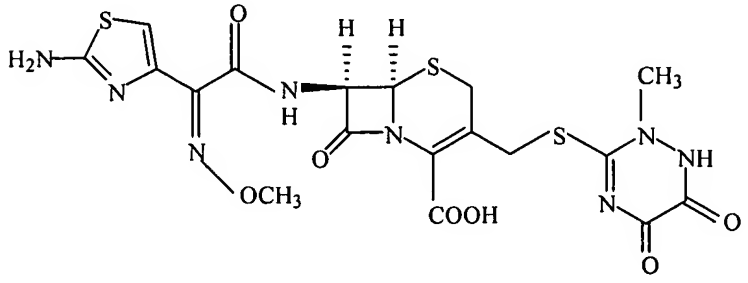
(V)

ii) desilylating the compound of formula (V), wherein X is as defined hereinabove to give the desilylated compound of formula (VI),



(VI)

iii) reacting the desilylated compound of formula (VI) with thiourea in a solvent system containing organic solvent and water, to obtain ceftriaxone of formula (I),

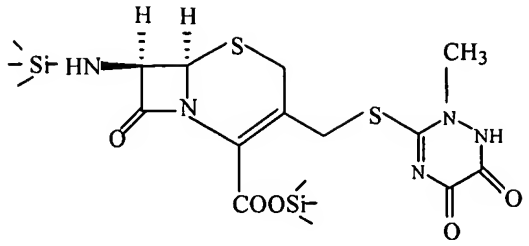


(I)

iv) converting the compound of formula (I) to the sodium salt (II);

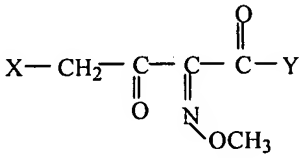
wherefore the improvement comprises

i[1]) reacting a silylated compound of formula (III),



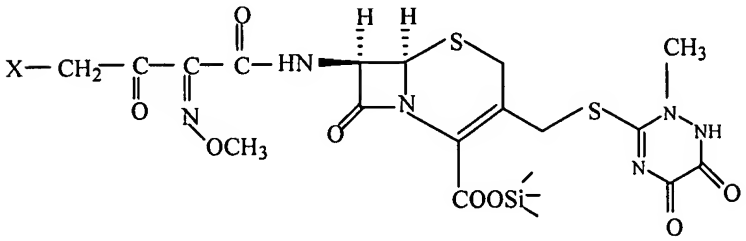
(III)

with a 4-halo-2-methoxyimino-3-oxo butyric acid derivative of formula (IV)[[,]] having a purity of at least 95% and containing di- and poly-brominated compounds less than 0.50%,



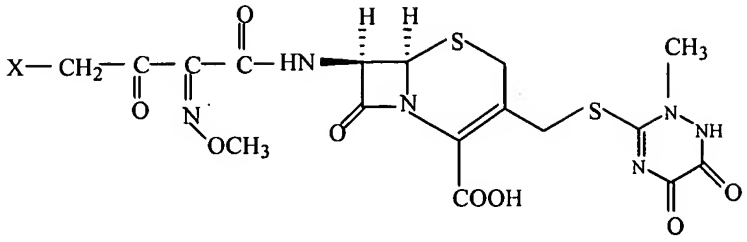
(IV)

wherein X and Y represent a halogen atom in the presence of an inert water-immiscible organic solvent or mixtures thereof and in the presence of an acid scavenging agent at a temperature of between -10° C to -0° C to give a compound of formula (V),



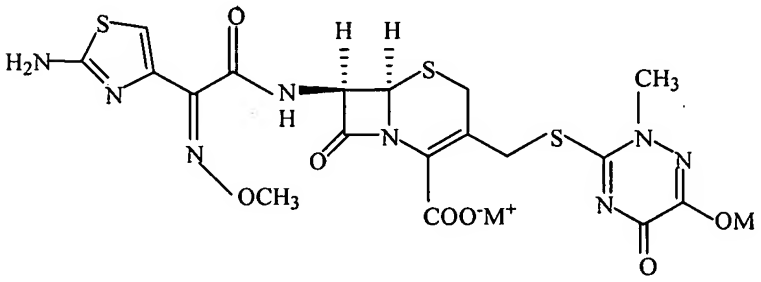
(V)

ii[1]) adding the solution of compound of formula (V) in the inert water-immiscible organic solvent or mixtures thereof to a 1:1 mixture of water and a water-immiscible organic solvent and separation of the organic phase to provide a solution of compound of formula (VI) in the inert water-immiscible organic solvent or mixtures thereof,



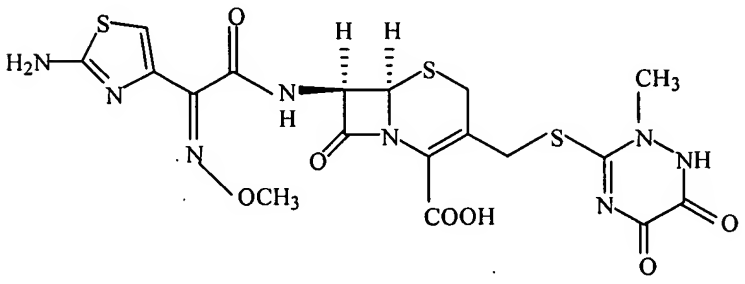
(VI)

iii[1]) reacting the solution of compound of formula (VI) in the inert water-immiscible organic solvent or mixtures thereof with a solution of thiourea in water in the presence of an alkali metal containing inorganic base at a temperature of between 0° C to +10° C at a pH ranging between 5.0 to 5.5 and separation of the organic layer to provide a solution of the alkali metal salt of ceftriaxone of formula (II[1]) in water, wherein M is an alkali metal,



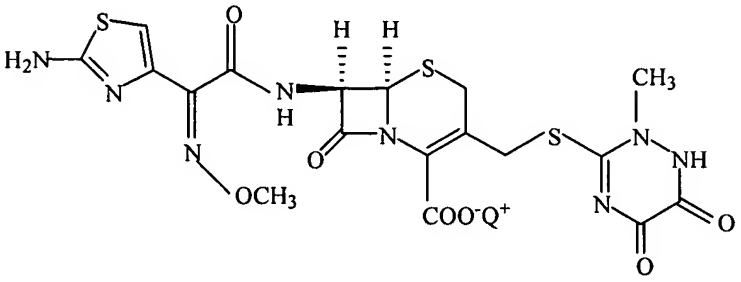
(II[1])

iv[1]) mixing the solution of the alkali metal salt of ceftriaxone (II'), wherein M is as defined hereinearlier in water with a water-immiscible organic solvent and a water-miscible solvent and treating the solution thus obtained with an acid to a pH of 3.6 to 4.0 and isolating the precipitated ceftriaxone of formula (I) by filtration,



(I)

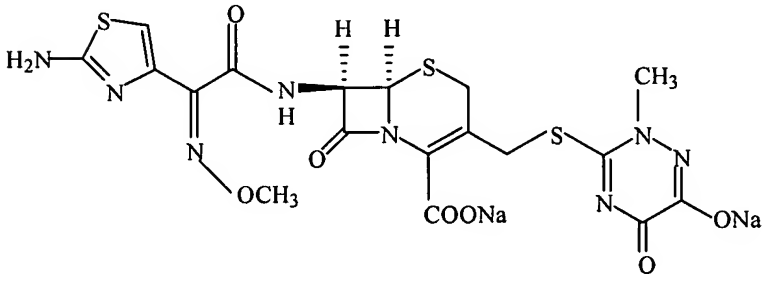
v[1]) reacting a solution of ceftriaxone of formula (I) in water with an organic amine maintaining a pH of 5.4 ± 0.2 to produce a solution of the amine salt of ceftriaxone in water of formula (VII),



(VII)

wherein Q^+ is QH^+ and represents the organic amine, and

vi[1]) reaction of the amine salt of ceftriaxone of formula (VII) in a mixture of water and a water-miscible organic solvent with a sodium metal ~~carrier~~ to give ceftriaxone sodium of formula (II)[[;]] ~~substantially free of impurities and having low Color absorbance.~~



(II)

Claim 2. (Original) A process according to claim 1, in which in step i[1]), the inert water-immiscible organic solvent is selected from chlorinated hydrocarbons, acetic acid (C_{1-4}) alkyl esters and ethers.

Claim 3. (Original) A process according to claim 1, in which in step i[1]), wherein the acid scavenging agent is selected from ethylene oxide, propylene oxide, butylene oxide, acetamide, epichlohydrin, calcium oxide, disodium hydrogen phosphate, calcium carbonate and quaternary ammonium phosphates.

Claim 4. (Currently Amended) A process according to any one of claims 1 and 2, wherein the ~~preferred~~ acid scavenging agent is acetamide.

Claim 5. (Original) A process according to any one of claims 1, 2 and 3, wherein the acid scavenging agent is employed in molar proportions of 1.0 to 3.0 moles per mole of compound of formula (III).

Claim 6. (Original) A process according to any one of claims 1, 2, and 3 [[and 4]], wherein the acid scavenging agent is employed in molar proportions of 1.0 to 1.5 moles per mole of compound of formula (III).

Claim 7. (Original) A process according to claim 1, in which in step ii[1]), the water-miscible organic solvent is selected from tetrahydrofuran or acetonitrile.

Claim 8. (Currently Amended) A process according to claim 1, in which in step iii[1]), thiourea is employed in molar proportions of 1.0 to 3.0 moles per mole of compound of formula (III), ~~preferably~~ in molar proportions of 1.0 to 1.5 moles per mole of compound of formula (III).

Claim 9. (Original) A process according to claim 1, in which in step iii[1]), the alkali metal inorganic base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate and lithium hydrogen carbonate.

Claim 10. (Currently Amended) A process according to any one of claims 1 and 9, wherein the alkali metal containing inorganic base is employed in molar proportions of 2.0 to 5.0 moles per mole of compound of formula (III), ~~preferably~~ in molar proportions of 2.0 to 3.0 moles per mole of compound of formula (III).

Claim 11. (Currently Amended) A process according to claim 1, in which in step iv[1]), the water-immiscible organic solvent is selected from chlorinated hydrocarbons, acetic acid (C_{1-4}) alkyl ~~esters and~~ ethers.

Claim 12. (Original) A process according to claim 1, in which in step iv[1]), the water-miscible organic solvent is selected from tetrahydrofuran, acetonitrile or a C_{1-4} lower alcohol.

Claim 13. (Original) A process according to claim 1, in which in step v[1]), the organic amine is selected from diethylamine, triethylamine, diisopropylamine, cyclohexylamine, pyridine, 2,4-dimethylamino pyridine and N-methyl morpholine.

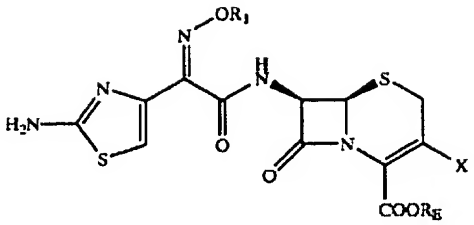
Claim 14. (Original) A process according to claim 1, in which in step vi[1]), the water-miscible organic solvent is selected from tetrahydrofuran, acetonitrile, a C_{1-4} lower alcohol and a ketonic solvent.

Claim 15. (Currently Amended) A process according to claim 1, in which in step vi[1]), the sodium metal ~~carrier carrier~~ is selected from sodium acetate, 2-ethyl sodium hexanoate and 2-ethyl sodium octanoate.

Claim 16. (Original) A process according to claim 1, wherein the ceftriaxone sodium of formula (II) has a Color absorbance of 0.04 to 0.05 AU at 450 nrn.

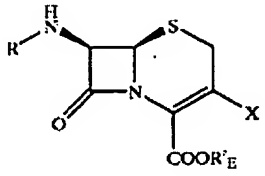
Claim 17. (Original) A process according to claim 1, wherein the level of total impurities in ceftriaxone sodium (II) obtained is the range of between 0.05 to 0.20%.

Claim 18. (Previously Presented) A process for the production of a compound of formula



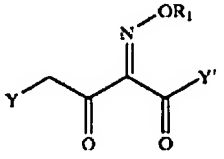
wherein X and R_1 are substituents useful in cephalosporin chemistry and R_E is hydrogen, a negative charge or together with the COO— group to which R_E is attached is an ester; comprising

i) reacting a compound of formula



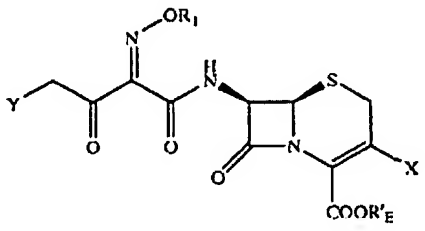
IV

wherein R is hydrogen or silyl, R'_E is silyl or together with the COO— group to which R_E is attached is an ester; and X is as defined above, with a compound of formula



III

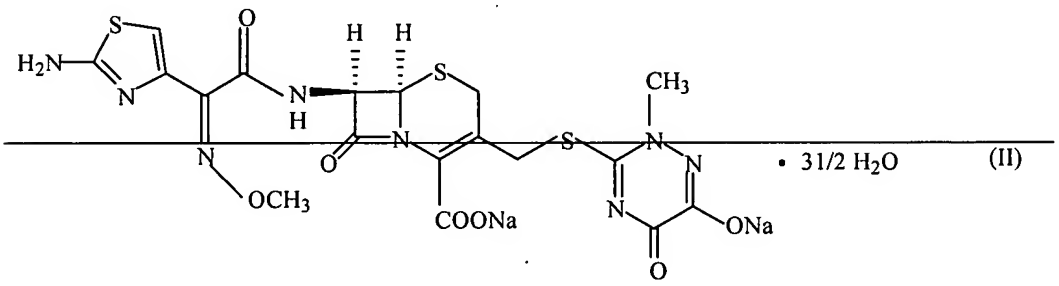
wherein Y is halogen, Y' is a group which forms a basis that a compound of formula III is in a reactive form; and R_1 is as defined above, to obtain a compound of formula



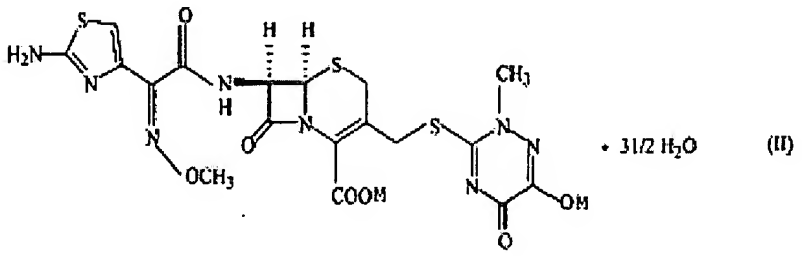
wherein Y, X, R'_E and R_1 are as defined above;

ii) desilylating a compound of formula II wherein Y, X, R'_E and R_1 are as defined above, and reacting a desilylated compound of formula II with thiourea in a solvent system containing organic solvent and water; to obtain a compound of formula I.

Claim 19. (Currently Amended) A process for preparation of ceftriaxone sodium of formula II,



(II)



(II)

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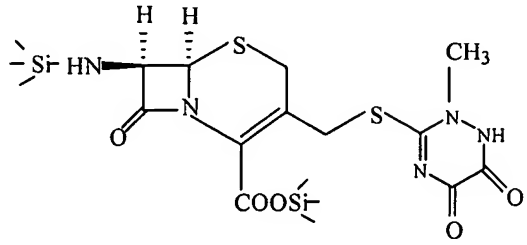
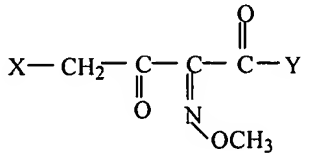
comprising the steps of:

i) reacting a silylated compound of formula III,



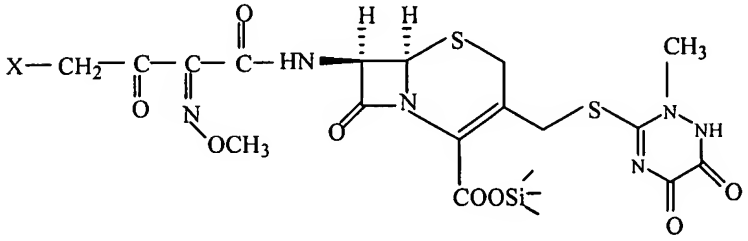
(III)

with a 4-halo-2-methoxyimino-3-oxo butyric acid derivative of formula IV, having a purity of at least 95% and containing di- and poly-brominated compounds less than 0.50%,



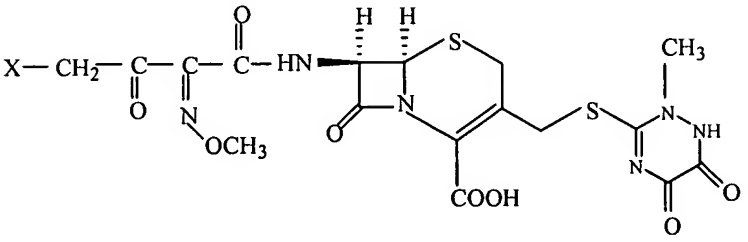
(IV)

wherein X and Y represent a halogen atom in the presence of an inert water-immiscible organic solvent or mixtures thereof and in the presence of an acid scavenging agent at a temperature of between -10° C to -0° C to give a compound of formula V,



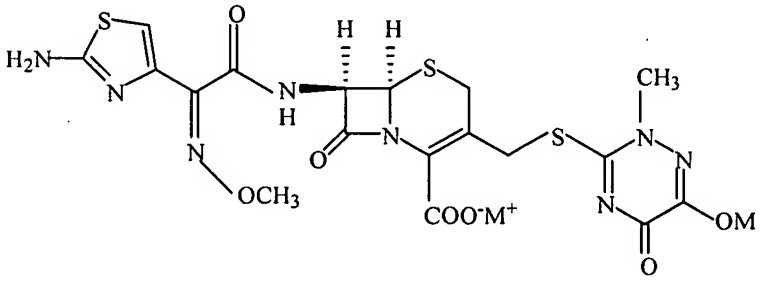
(V)

ii) adding the solution of compound of formula V in the inert water-immiscible organic solvent or mixtures thereof to a 1:1 mixture of water and a water-immiscible organic solvent and separation of the organic phase to provide a solution of compound of formula VI in the inert water-immiscible organic solvent or mixtures thereof,



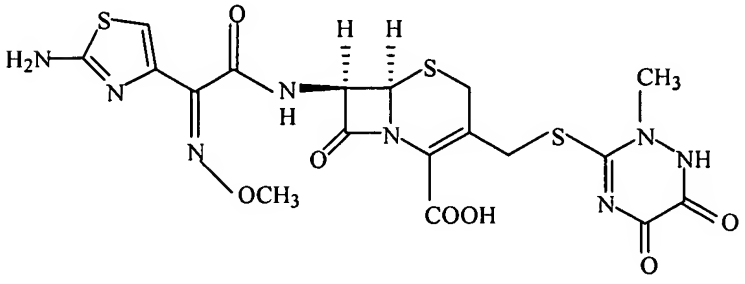
(VI)

iii) reacting the solution of compound of formula VI in the inert water-immiscible organic solvent or mixtures thereof with a solution of thiourea in water in the presence of an alkali metal containing inorganic base at a temperature of between 0° C to +10° C at a pH ranging between 5.0 to 5.5 and separation of the organic layer to provide a solution of the alkali metal salt of ceftriaxone of formula II in water, wherein M is an alkali metal,



(II[1])

Claim 20. (Previously presented) The process according to claim 19, further comprising the step of mixing the solution of the alkali metal salt of ceftriaxone of the formula II, wherein M is as defined hereinearlier in water with a water-immiscible organic solvent and a water-miscible solvent and treating the solution thus obtained with an acid to a pH of 3.6 to 4.0 and isolating the precipitated ceftriaxone of formula I

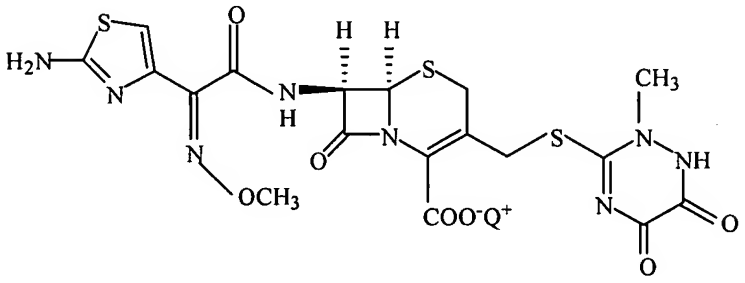


(I)

by filtration.

Claim 21. (Currently Amended) The process according to claim 20, further comprising the step of reacting a solution of ceftriaxone of formula I in water

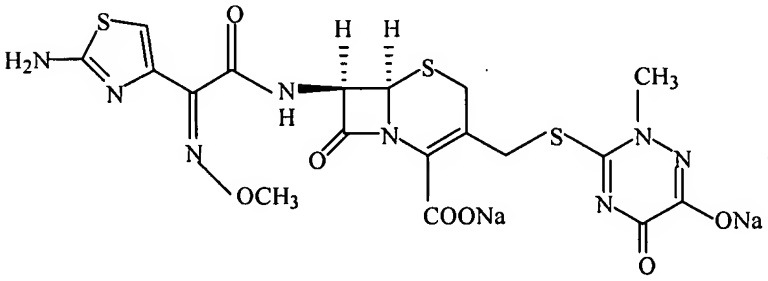
with an organic amine maintaining a pH of 5.4 ± 0.2 to produce a solution of the amine salt of ceftriaxone in water of formula VII,



(VII)

wherein Q^+ is QH^+ and represents the organic amine.

Claim 22. (Currently Amended) The process according to claim 21, further comprising the step of reacting an amine salt of ceftriaxone of formula VII in a mixture of water and a water-miscible organic solvent with a sodium metal ~~carrier~~ to give ceftriaxone sodium of formula II



• 31/2 H_2O (II)

substantially free of impurities and having low color absorbance.